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inhibitors such as beta adrenergic blocking agents combined with antiplatelets such as aspirin." Presuming that the Office simply misspoke its statement that beta adrenergic blockers are examples of vasopeptidase inhibitors and that the Office meant to state that Powell et al. teach vasopeptidase inhibitors combined with beta adrenergic blocking agents and antiplatelet agents, Applicants respectfully traverse.

An accidental or unwitting duplication of an invention cannot constitute an anticipation. In re Felton, 484 F.2d 495, 179 USPQ 295 (CCPA 1973); citing Tilghman v. Proctor, 102 U.S. 707 (1880) and Eibel Process Co. v. Minnesota and Ontario Paper Co., 261 U.S. 45 (1923). In light of the following arguments and evidence, Powell et al. disclosure is an unwitting duplication of Applicants' invention.

Vasopeptidase inhibitor and omapatrilat, as taught by Powell et al., in combination with a beta-adrenergic blocking agent would result in a dosage unit that inherently has added risk for an individual with cardiovascular disease. The use of vasopeptidase inhibitors increases the risk of angioedema. Angioedema is characterized by swelling of the tissues such as the skin and the gastrointestinal and respiratory tracts. Involvement of the airway with swelling causing closure can be life threatening. Angioedema relates to allergic conditions in which the adrenergic pathways are impaired. Treatments include adrenergic stimulatory agents such as epinephrine. In fact, the ACE inhibitor Zestril (See PDR 2001, page 656; attached as Exhibit 1) carries the warning ". . . angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx likely to cause airway obstruction, appropriate therapy, e.g. subcutaneous epinephrine solution

1:1000 (0.30 ml to 0.5 ml) and/or measures necessary to ensure a patient airway should be promptly provided."

Other studies have ascertained this added risk. Experience with the vasopeptidase inhibitor, omapatrilat, is reported by A. Coates in Omapatrilat – the story of Overture and Octave, International Journal of Cardiology, November 2002, 86(1):1. (See Exhibit 2). Significantly more cases of angioedema were seen with Omapatrilat than with enalapril. Overall death rates were similar and all adverse events were similar. The rates of angioedema were much higher in blacks and for smokers. In summary, Coates states that "we were left with a drug that was, for heart failure, not superior to an ACE inhibitor already off patent, and, as an anti-hypertensive, with an angioedema rate more than double that of an ACE inhibitor in a large head to head comparison."

In another study, a clinical perspective and reassessment of the mechanisms for angioedema caused by other inhibitors of the renin-angiotensin system was considered by A.G. Chiu, E.J. Krowiak and Z.E. Deeb in Angioedema associated with angiotensin II receptor antagonists: challenging our knowledge of angioedema and its etiology, Laryngoscope, October 2001, 111(10), 1729-1731. (See Exhibit 3). The authors review the literature and report three cases of AT2 receptor antagonist-induced angioedema, one which required surgical airway intervention. The authors state that angioedema is a potentially life-threatening condition commonly associated with ACE inhibitor use. They further state that the incidence of AT2 blocker-induced angioedema brings into question prior theories on the etiology of angioedema and its pathogenesis.

Applicants note that angioedema is yet more common with vasopeptidase inhibitors. Applicants further point out the potential for vasopeptidase inhibitor-induced angioedema is worsened by the combination of a vasopeptidase inhibitor with a beta-adrenergic blocking agent. The concomitant use of adrenergic blocking agents with vasopeptidase inhibitors increases the potential for angioedema to occur and the likelihood for more severe and intractable angioedema, and decreases the efficacy of rescue treatments with adrenergic stimulatory agents. The beta-blocker Ternomin (PDR 2001, page 650; attached as Exhibit 4) discloses the precaution that "while taking beta blockers, patients with a history of anaphylactic reaction may have a more severe reaction and such patients may be unresponsive to the usual doses of epinephrine used to treat the allergic reaction." The beta-blocker Indereal (PDR 2001, page 3379; attached as Exhibit 5) carries a similar warning.

The results of aspirin therapy are well known and documented in Applicants' specification. The results of beta-blocker therapy are likewise documented and further reflected in Applicants' previous literature submissions. Applicants assert that these protective results clearly contrast those that would be anticipated from treating individuals with cardiovascular disease with a combination that would place them at risk from serious side effects requiring cardiac-stimulatory medications such as epinephrine to reverse such side effects. **Such a combination would be the antithesis of protective.** In view of this contradiction, Powell et al. disclosure contains only an accidental or unwitting duplication of Applicants' invention and, thus, cannot constitute an anticipation.

Further support for such a conclusion can be found in the fact that Powell et al. claim only the combination of a vasopectidase inhibitor and a single pharmaceutially active agent (See Claim 4). Claim 9 further limits the choice to a single agent by using alternative claim language. Claims 14 and 16 further limit the combination to a vasopectidase inhibitor and aspirin.

Powell et al. fail to disclose a combination of anti-adrenergic and anti-platelet agents without a vasopectidase inhibitor. The use of vasopectidase inhibitors increases the risk for a more severe and intractable angioedema for which the usual doses of an andrenergic stimulatory agent may be insufficient because of the combination of the vasopectidase inhibitor with an anti-adrenergic agent. It is clear from the Powell et al. disclosure and claims and the increased risks associated with vasopectidase inhibitors that the reference to "one or more pharmaceutically active agents" in Column 2 is only an accidental or unwitting duplication of Applicants' invention and, thus, cannot constitute an anticipation.

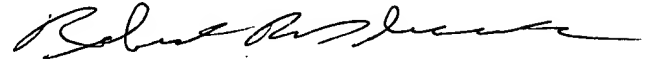
In light of Applicants' amendments and the arguments presented, Applicants respectfully submit that the 35 USC §102(a) rejection of Claims 1-7, 9-11 and 13-17 has been successfully traversed. Allowance is therefore requested.

Applicants believe that all of the pending claims should now be in condition for allowance. Early and favorable action is respectfully requested.

The Examiner is invited to telephone the undersigned, Applicant's attorney of record, to facilitate advancement of the present application.

Respectfully submitted,

Dated: 11/25/02



Robert R. Deleault, Reg. No. 39,165  
Attorney for Applicants  
41 Brook Street  
Manchester, NH 03104  
Tel. (603) 668-1971

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November 20, 2002  
Robert R. Deleault  
Robert R. Deleault

**Version with markings to show changes made**

Claim 1 has been amended as follows:

1. (Twice Amended) A medicament dosage unit consisting essentially of a beta-adrenergic blocker and a platelet inhibitor together in a single dosage unit quantity sufficient to provide a cardiovascular protective dosage.

Claim 9 has been amended as follows:

9. (Twice Amended) A method of treating cardiovascular disease said method comprising:  
  
formulating a single dosage unit consisting essentially of a beta-adrenergic blocking agent and a platelet inhibitor in a single dosage unit quantity sufficient to provide a cardiovascular protective dosage; and  
  
administering said single dosage unit to a patient.

Claim 14 has been amended as follows:

14. (Amended) A method of making a cardiovascular protective dosage unit comprising formulating a single dosage unit consisting essentially of a beta-adrenergic blocking agent and a platelet inhibitor in a quantity sufficient to provide a cardiovascular protective dosage.

Claim 16 has been amended as follows:

16. (Amended) A medicament dosage unit consisting essentially of a beta-adrenergic blocker and aspirin combined in a single dosage unit in sufficient quantity to provide a cardiovascular protective dosage.



066/ASTRAZENECA

Exhibit + 10

**Zestril—Cont.**

single daily doses, the effect was more consistent and the mean effect was considerably larger in some studies with doses of 20 mg or more than with lower doses. However, at all doses studied, the mean antihypertensive effect was substantially smaller 24 hours after dosing than it was 6 hours after dosing.

In some patients achievement of optimal blood pressure reduction may require two to four weeks of therapy.

The antihypertensive effects of ZESTRIL are maintained during long-term therapy. Abrupt withdrawal of ZESTRIL has not been associated with a rapid increase in blood pressure, or a significant increase in blood pressure compared to pretreatment levels.

Two dose-response studies utilizing a once daily regimen were conducted in 448 mild to moderate hypertensive patients not on a diuretic. Blood pressure was measured 24 hours after dosing. An antihypertensive effect of ZESTRIL was seen with 5 mg in some patients. However, in both studies blood pressure reduction occurred sooner and was greater in patients treated with 10, 20 or 60 mg of ZESTRIL. In controlled clinical studies, ZESTRIL 20-60 mg has been compared in patients with mild to moderate hypertension to hydrochlorothiazide 12.5-50 mg and with atenolol 50-200 mg; and in patients with moderate to severe hypertension to metoprolol 100-200 mg. It was superior to hydrochlorothiazide in effects on systolic and diastolic pressure in a population that was 3/4 Caucasian. ZESTRIL was approximately equivalent to atenolol and metoprolol in effects on diastolic blood pressure, and had somewhat greater effects on systolic blood pressure.

ZESTRIL had similar effectiveness and adverse effects in younger and older (> 65 years) patients. It was less effective in blacks than in Caucasians.

In hemodynamic studies in patients with essential hypertension, blood pressure reduction was accompanied by a reduction in peripheral arterial resistance with little or no change in cardiac output and in heart rate. In a study in nine hypertensive patients, following administration of ZESTRIL, there was an increase in mean renal blood flow that was not significant. Data from several small studies are inconsistent with respect to the effect of lisinopril on glomerular filtration rate in hypertensive patients with normal renal function, but suggest that changes, if any, are not large.

In patients with renovascular hypertension ZESTRIL has been shown to be well tolerated and effective in controlling blood pressure. (See PRECAUTIONS.)

**Heart Failure:** During baseline-controlled clinical trials, in patients receiving digoxin and diuretics, single doses of ZESTRIL resulted in decreases in pulmonary capillary wedge pressure, systemic vascular resistance and blood pressure accompanied by an increase in cardiac output and no change in heart rate.

In two placebo controlled, 12-week clinical studies, using doses of ZESTRIL up to 20 mg, ZESTRIL as adjunctive therapy to digoxin and diuretics improved the following signs and symptoms due to congestive heart failure: edema, rales, paroxysmal nocturnal dyspnea and jugular venous distention. In one of the studies, beneficial response was also noted for orthopnea, presence of third heart sound and the number of patients classified as NYHA Class III and IV. Exercise tolerance was also improved in this study. The once daily dosing for the treatment of congestive heart failure was the only dosage regimen used during clinical trial development and was determined by the measurement of hemodynamic response. A large (over 8000 patients) survival study, the ATLAS Trial, comparing 2.5 and 36 mg of lisinopril in patients with heart failure, showed that the higher dose of lisinopril had outcomes at least as favorable as the lower dose.

**Acute Myocardial Infarction:** The Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI-3) study was a multicenter, controlled, randomized, unblinded clinical trial conducted in 19,394 patients with acute myocardial infarction admitted to a coronary care unit. It was designed to examine the effects of short-term (6 week) treatment with lisinopril, nitrates, their combination, or no therapy on short-term (6 week) mortality and on longer-term death and markedly impaired cardiac function. Patients presenting within 24 hours of the onset of symptoms who were hemodynamically stable were randomized, in a 2 x 2 factorial design, to six weeks of either: 1) ZESTRIL alone (n=4841), 2) nitrates alone (n=4869), 3) ZESTRIL plus nitrates (n=4841), or 4) open control (n=4848). All patients received routine therapies, including thrombolytics (72%), aspirin (84%), and a beta-blocker (81%), as appropriate, normally utilized in acute myocardial infarction (MI) patients. The protocol excluded patients with hypotension (systolic blood pressure < 100 mmHg), severe heart failure, cardiogenic shock, and renal dysfunction (serum creatinine > 3 mg/dL and/or proteinuria > 500 mg/24 h). Doses of ZESTRIL were adjusted as necessary according to protocol (see DOSAGE AND ADMINISTRATION).

Study treatment was withdrawn at six weeks except where

Patients receiving ZESTRIL (n=9648), alone or with nitrates, had an 11% lower risk of death (Sp [two-tailed] = 0.04) compared to patients receiving no ZESTRIL (n=9672) (6.4% vs. 7.3%, respectively) at six weeks. Although patients randomized to receive ZESTRIL for up to six weeks also fared numerically better on the combined end-point at 6 months, the open nature of the assessment of heart failure, substantial loss to follow-up echocardiography, and substantial excess use of lisinopril between 6 weeks and 6 months in the group randomized to 6 weeks of lisinopril, preclude any conclusion about this endpoint.

Patients with acute myocardial infarction, treated with ZESTRIL, had a higher (9.0% versus 8.7%) incidence of persistent hypotension (systolic blood pressure < 90 mmHg for more than 1 hour) and renal dysfunction (2.4% versus 1.1%) in-hospital and at six weeks (increasing creatinine concentration to over 3 mg/dL or a doubling or more of the baseline serum creatinine concentration). See ADVERSE REACTIONS—Acute Myocardial Infarction.

**INDICATIONS AND USAGE**

**Hypertension:** ZESTRIL is indicated for the treatment of hypertension. It may be used alone as initial therapy or concomitantly with other classes of antihypertensive agents.

**Heart Failure:** ZESTRIL is indicated as adjunctive therapy in the management of heart failure in patients who are not responding adequately to diuretics and digitalis.

**Acute Myocardial Infarction:** ZESTRIL is indicated for the treatment of hemodynamically stable patients within 24 hours of acute myocardial infarction, to improve survival. Patients should receive, as appropriate, the standard recommended treatments such as thrombolytics, aspirin and beta-blockers.

In using ZESTRIL, consideration should be given to the fact that another angiotensin converting enzyme inhibitor, captopril, has caused agranulocytosis, particularly in patients with renal impairment or collagen vascular disease, and that available data are insufficient to show that ZESTRIL does not have a similar risk. (See WARNINGS.)

In considering the use of ZESTRIL, it should be noted that in controlled trials ACE inhibitors have an effect on blood pressure that is less in black patients than in nonblacks. In addition, ACE inhibitors have been associated with a higher rate of angioedema in black than in nonblack patients (see WARNINGS, Angioedema).

**CONTRAINDICATIONS**

ZESTRIL is contraindicated in patients who are hypersensitive to this product and in patients with a history of angioedema related to previous treatment with an angiotensin converting enzyme inhibitor.

**WARNINGS**

**Anaphylactoid and Possibly Related Reactions:** Presumably because angiotensin-converting enzyme inhibitors affect the metabolism of eicosanoids and polypeptides, including endogenous bradykinin, patients receiving ACE inhibitors (including ZESTRIL) may be subject to a variety of adverse reactions, some of them serious.

**Angioedema:** Angioedema of the face, extremities, lips, tongue, glottis and/or larynx has been reported in patients treated with angiotensin converting enzyme inhibitors, including ZESTRIL. This may occur at any time during treatment. ACE inhibitors have been associated with a higher rate of angioedema in black than in nonblack patients. ZESTRIL should be promptly discontinued and appropriate therapy and monitoring should be provided until complete and sustained resolution of signs and symptoms has occurred. In instances where swelling has been confined to the face and lips the condition has generally resolved without treatment, although antihistamines have been useful in relieving symptoms. Angioedema associated with laryngeal edema may be fatal. Where there is involvement of the tongue, glottis or larynx, likely to cause airway obstruction, appropriate therapy, e.g., subcutaneous epinephrine solution 1:1000 (0.3 mL to 0.5 mL) and/or measures necessary to ensure a patent airway should be promptly provided. (See ADVERSE REACTIONS.)

Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor. (See also INDICATIONS AND USAGE AND CONTRAINDICATIONS.)

**Anaphylactoid Reactions During Desensitization:** Two patients undergoing desensitizing treatment with hymenoptera venom while receiving ACE inhibitors sustained life-threatening anaphylactoid reactions. In the same patients, these reactions were avoided when ACE inhibitors were temporarily withheld, but they reappeared upon inadvertent rechallenges.

**Anaphylactoid Reactions During Membrane Exposure:** Sudden and potentially life-threatening anaphylactoid reactions have been reported in some patients dialyzed with high-flux membranes (e.g., AN694) and treated concomitantly with an ACE inhibitor. In such patients, dialysis must be stopped immediately, and aggressive therapy for anaphylactoid reactions be initiated. Symptoms have not been relieved by antihistamines in these situations. In these patients, consideration should be given to using a different type of dialysis membrane or a different class of antihyper-

Patients with heart failure given ZESTRIL some reduction in blood pressure, with pe reduction occurring 6 to 8 hours post do the two-dose ATLAS trial suggested that tension may increase with dose of lisinop patients. Discontinuation of therapy bec symptomatic hypotension usually is no dosing instructions are followed; caution when initiating therapy. (See DOSAG TRATION.)

Patients at risk of excessive hypotension ated with oliguria and/or progressive az with acute renal failure and/or death, inc following conditions or characteristics: systolic blood pressure below 100 mm high dose diuretic therapy; recent inten crease in diuretic dose; renal dialysis and/or salt depletion of any etiology. It eliminate the diuretic dose or increa tiously before initiating therapy with Z at risk for excessive hypotension who such adjustments. (See PRECAUTION: AND ADVERSE REACTIONS.)

Patients with acute myocardial infarct trial had a higher (9.0% versus 8.7%) in hypotension (systolic blood pressure < than 1 hour) when treated with ZEST ZESTRIL must not be initiated in acv tion patients at risk of further serious oration after treatment with a vaso blood pressure at 100 mmHg or lower)

In patients at risk of excessive hypote be started under very close medical i patients should be followed closely for treatment and whenever the dose of uretic is increased. Similar considerat tients with ischemic heart or cerebro patients with acute myocardial infar cessive fall in blood pressure could r infarction or cerebrovascular accident If excessive hypotension occurs, ti placed in the supine position and, if intravenous infusion of normal saline sive response is not a contraindication ZESTRIL which usually can be given the blood pressure has stabilized. If sion develops, a dose reduction i ZESTRIL or concomitant diuretic m Leukopenia/Neutropenia/Agranulo giostensin converting enzyme inhibit shown to cause agranulocytosis and sion, rarely in uncomplicated patien in patients with renal impairment have a collagen vascular disease. Av cal trials of ZESTRIL are insufficient does not cause agranulocytosis at si experience has revealed rare cases nia and bone marrow depression in ship to lisinopril cannot be excluded white blood cell counts in patients disease and renal disease should be Hepatic Failure: Rarely, ACE inhi ated with a syndrome that starts e and progresses to fulminant hep times) death. The mechanism of thi stood. Patients receiving ACE inhi dice or marked elevations of hepatic tinue the ACE inhibitor and reced follow-up.

**Fetal/Neonatal Morbidity and Mo** can cause fetal and neonatal morbi ministered to pregnant women. S been reported in the world literat detected, ACE inhibitors should be possible.

The use of ACE inhibitors during mesters of pregnancy has been a neonatal injury, including hypoten plasia, anuria, reversible or irrev death. Oligohydramnios has also b resulting from decreased fetal re nio in this setting has been asoc tructures, craniofacial deformati development. Prematurity, intraul and patent ductus arteriosus ha though it is not clear whether the the ACE-inhibitor exposure.

These adverse effects do not app intrauterine ACE-inhibitor expo to the first trimester. Mothers w are exposed to ACE inhibitors on ter should be so informed. None come pregnant, physicians shou continue the use of ZESTRIL as Rarely (probably less often the pregnancies), no alternative to Af in these rare cases, the mothers

# Exhibit 2

1: Int J Cardiol 2002 Nov;86(1):1

Omapatrilat- the story of Overture and Octave.

Coats A.

Viscount Royston Professor of Clinical Cardiology, National Heart and Lung Institute, Imperial College School of Medicine, at Royal Brompton Hospital, Sydney St., SW3 6NP, London, UK

At the American College of Cardiology in March two major trials were presented. The publicity surrounding the two could not have been more different. The LIFE demonstrated clear superiority of losartan-based therapy over atenolol-based therapy for the treatment of hypertension. It was published the same week in the Lancet and received major press coverage all over the world. The OVERTURE (Omapatrilat Versus Enalapril Randomized Trial of Utility in Reducing Events) study in contrast received a subdued reception, very little publicity and is yet to be published. 5770 NYHA class II-IV heart failure patients (LVEF  $\leq$  30%, recent heart failure hospital admission) were randomised and uptitrated to either 10 mg BD of Enalapril or 40 mg once a day Omapatrilat. The primary end-point of all cause mortality or heart failure related hospitalisation did not differ significantly: 914/2884 for Enalapril and 914/2886 for Omapatrilat (hazard ratio 0.94, CI's 0.86-1.03,  $P=0.187$ ). Mortality was also similar: 509 for Enalapril and 477 for Omapatrilat (hazard ratio 0.94, CI's 0.83-1.07,  $P=0.339$ ). Omapatrilat was as good as Enalapril but not better. The worrying trend was however, that angioedema was more common with Omapatrilat; 24 (0.8%) versus 14 cases (0.5%). The OCTAVE (Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril) study was also presented at this time. 25,267 hypertensives were randomised to Omapatrilat or enalapril and a difference of approximately 3 mmHg in favour of Omapatrilat was seen. Significantly more cases of angioedema were seen with Omapatrilat, 274 (2.17%) compared to 86 (0.68%) with enalapril. Overall death rates were similar, 0.18% for enalapril and 0.15% for Omapatrilat. All adverse events were similar, 51.0% for Omapatrilat and 50.4% for enalapril. The rates of angioedema were much higher in blacks, 5.54% for Omapatrilat and 1.62% for enalapril and for smokers, 3.93% for Omapatrilat and 0.81% for enalapril. We were left with a drug that was, for heart failure, not superior to an ACE inhibitor already off patent, and, as an anti-hypertensive, with an angioedema rate more than double that of an ACE inhibitor in a large head to head comparison. The medical community will be watching to make sure these data are published in full in the medical literature in a timely fashion, in the order of end-points specified in the protocol and with appropriate emphasis on the logical points of presentation.

PMID: 12243845 [PubMed - in process]

# Exhibit 3

1: Laryngoscope 2001 Oct;111(10):1729-31

Angioedema associated with angiotensin II receptor antagonists: challenging our knowledge of angioedema and its etiology.

Chiu AG, Krowiak EJ, Deeb ZE.

Department of Otolaryngology--Head and Neck Surgery, The Washington Hospital Center and Georgetown University Medical Center, Washington DC, USA.  
Alexchiu11@hotmail.com

**INTRODUCTION:** Use of angiotensin converting enzyme inhibitors has long been associated with angioedema. Increased levels of bradykinin caused by the inhibition of angiotensin converting enzyme have been thought to be responsible for this side effect. Angiotensin II receptor antagonists (AT2 blockers), such as losartan potassium (Cozaar; Merck & Co., West Point, PA), are a new class of antihypertensives developed in part to eliminate cough and angioedema associated with ACE inhibitors. These agents act by selectively binding to angiotensin II receptor sites, thereby eliminating the hypertensive effects of angiotensin without affecting local and systemic bradykinin levels. We present three cases of AT2 receptor antagonist-induced angioedema, and examine its significance in the treatment of angioedema and its proposed etiology. **METHODS:** A retrospective chart review and review of the literature. **RESULTS:** Three patients taking the AT2 blocker losartan presented with mucosal swelling in the head and neck clinically consistent with angioedema. All three patients had prior episodes of angioedema while on losartan. Two patients presented with involvement of the anterior tongue and face that resolved within 12 hours of discontinuation of the losartan and a course of intravenous steroids. The third patient experienced recurring episodes of angioedema that eventually required a tracheotomy for airway compromise. After discontinuing the losartan and receiving a course of intravenous steroids, the angioedema resolved in 5 days. The patient was decannulated 10 days after onset of symptoms. **CONCLUSION:** Angioedema is a potentially life-threatening condition commonly associated with ACE inhibitor use. AT2 blockers bind to angiotensin II receptor sites and have no demonstrable effect on local or systemic bradykinin levels. We present three cases that demonstrate AT2 blocker-induced angioedema. They were all complicated by the fact that the inciting agent, losartan, was not discontinued after the initial episode and resulted in recurrent episodes of angioedema, one of which required surgical airway intervention. The incidence of AT2 blocker-induced angioedema brings into question prior theories on the etiology of angioedema and bradykinin's role in its pathogenesis.

PMID: 11801934 [PubMed - indexed for MEDLINE]



